Handouts for Participants:

Vitamin D Deficiency:

How it Relates to Patients with Developmental Disabilities and Ways to Correct it

"Vitamin D Symposium"

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The Health Benefits of Vitamin D for Non-Skeletal Effects for Those with Developmental Disabilities

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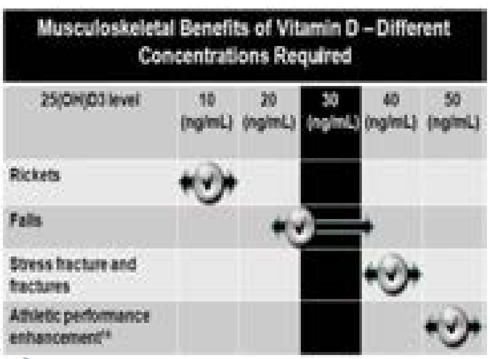
- The Vitamin D Society (Canada).

Outline

- Vitamin D and reduction and/or treatment of
  - Physical functioning
  - Dental caries
  - Respiratory infections
  - Diabetes mellitus
  - Cardiovascular disease
  - Cancer
  - Neuroprotection
  - Autism
  - Mortality rates
  - Randomized controlled trials
  - Recommendations
  - Sources for additional information

Physical Functioning

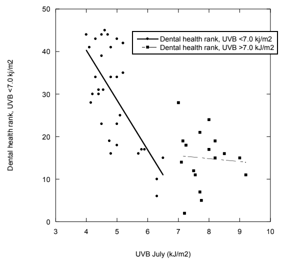
- Numerous studies, particularly in the German literature in the 1950s, show vitamin D-producing ultraviolet light improves athletic performance. Furthermore, a consistent literature indicates physical and athletic performance is seasonal; it peaks when 25-hydroxy-vitamin D [25(OH)D] levels peak, declines as they decline, and reaches its nadir when 25(OH)D levels are at their lowest. Vitamin D also increases the size and number of Type II (fast twitch) muscle fibers. Most cross-sectional studies show that 25(OH)D levels are directly associated with musculoskeletal performance in older individuals. Most randomized controlled trials, again mostly in older individuals, show that vitamin D improves physical performance.
- Cannell JJ, Hollis BW, Sorenson MB, Taft TN, Anderson JJ. Athletic performance and vitamin D. Med Sci Sports Exerc. 2009 May;41(5):1102-10.



Dental Caries

- Dental caries are caused by oral bacteria.
- Vitamin D, through induction of cathelicidin, reduces concentration of oral bacteria.
- This was first shown in a study of vitamin D2 supplementation in 1928 by May Mellanby.
- Several recent studies identified cathelicidin as a way to reduce dental caries.
- Grant WB. A review of the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries. Dermatoendocrinol. 2011;3(3):193-198.

Dental Rank vs. Solar UVB Dose in July, Men Entering WWI and WWII



State averaged data

Dental Caries – Vitamin D Trials

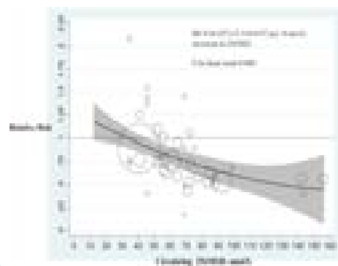
- Vitamin D has been used to prevent and treat dental caries. The objective of this study was to conduct a systematic review of controlled clinical trials (CCTs) assessing the impact of vitamin D on dental caries prevention. Twenty-four CCTs encompassing 2,827 children met the inclusion criteria.
- The pooled relative-rate estimate of supplemental vitamin D was 0.53 (95% CI, 0.43–0.65).

- Hujoel PP. Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis. Nutrition Reviews. 2013 Feb;71(2):88-97.

Respiratory Infections

- Vitamin D induces production of cathelicidin, which has antimicrobial properties.
- Higher 25(OH)D levels have been found associated with reduced risk of acute respiratory infections, and pneumonia.
- A randomized controlled trial on schoolchildren in Japan using 1100 IU/d vitamin D3 found a 67% reduction for influenza type A for those not using any other vitamin D supplements compared to 200 IU/d. [Urishama, 2010]

Diabetes Mellitus Type 2



Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, Hu FB. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care. 2013 May;36(5):1422-8.

Divide by 2.5 for ng/mL

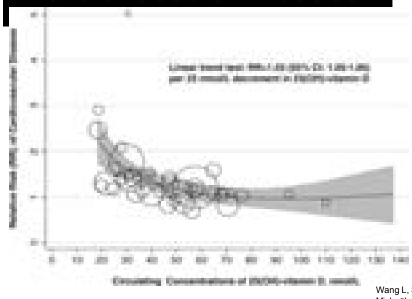
Insulin Resistance

- Insulin resistance is the condition in which cells do not respond to insulin, resulting in hyperglycemia. A vitamin D RCT involving insulin-resistant South Asian women living in New Zealand with baseline 25(OH)D levels below 20 ng/mL gave half of the women 4000 IU/d of vitamin D3. Participants reaching serum 25(OH)D levels of 32 to 48 ng/mL showed significantly improved insulin sensitivity.
- vonHurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial. *Br J Nutr* 2010;103:549-55

Cardiovascular Disease

- The active metabolite of vitamin D, 1α,25-dihydroxyvitamin D, binds to the vitamin D receptor that regulates numerous genes involved in fundamental processes of potential relevance to cardiovascular disease, including cell proliferation and differentiation, apoptosis, oxidative stress, membrane transport, matrix homeostasis, and cell adhesion. Vitamin D receptors have been found in all the major cardiovascular cell types including cardiomyocytes, arterial wall cells, and immune cells. Experimental studies have established a role for vitamin D metabolites in pathways that are integral to cardiovascular function and disease, including inflammation, thrombosis, and the renin-angiotensin system. Clinical studies have generally demonstrated an independent association between vitamin D deficiency and various manifestations of degenerative cardiovascular disease including vascular calcification.

- Norman PE, Powell JT. Vitamin D and cardiovascular disease. Circ Res. 2014 Jan 17;114(2):379-93.



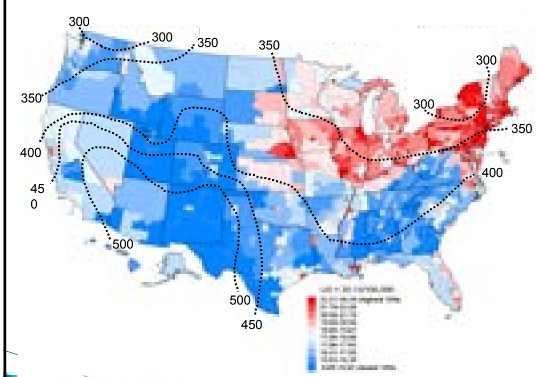
Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes. 2012 Nov 1;5(6):819-29.

Cancer – Mechanisms

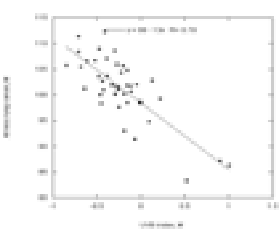
- Effects on cellular differentiation and proliferation
- Maintains epithelial cell integrity and tight junctions between cells
- Increased calcium absorption
- Anti-angiogenesis
- Anti-metastasis
- The beneficial effects of vitamin D on cancer appear to be stronger for progression and metastasis than for incidence.

Ecological Studies of UVB, Vitamin D, Cancer

- The first epidemiological study hypothesizing that solar UVB, through production of vitamin D, reduced the risk of cancer was an ecological study published in 1980.
- The brothers Cedric Garland and Frank Garland, beginning graduate students at Johns Hopkins School of Public Health in 1974, looked at the map of colon cancer mortality rates in the U.S. and saw a link to solar radiation.

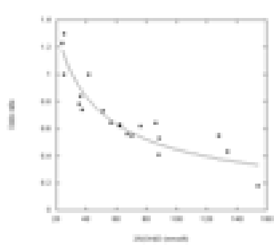


Occupational Study of Cancer Incidence in Nordic Countries



Grant WB. Role of solar UV irradiance and smoking in cancer as inferred from cancer incidence rates by occupation in Nordic countries. Dermatoendocrinol. 2012;4(2):203-11.

Meta-Analysis of Breast Cancer Risk with Respect to Diagnostic Serum 25(OH)D



Based on five case-control studies from Germany, Mexico, UK, and USA

Grant WB. A review of the evidence regarding the solar ultraviolet-B-vitamin D-cancer hypothesis. Standardy Medyczne/ Pediatria. 2012;9:610-9.

16 Vitamin D-Sensitive Cancers (from several ecological studies)

- Gastrointestinal: colon, esophageal,
- gallbladder, gastric, pancreatic, rectal
- Urinary: bladder, kidney
- Male: prostate (but U-shaped?)
- Female: breast, (endometrial), (ovarian),
- vulvar
- Blood: Hodgkin's and non-Hodgkin's lymphoma, (leukemia)

Neuroprotection

- "The conflation of in vitro, ex vivo, and animal model data provide compelling evidence that vitamin D has a crucial role in proliferation, differentiation, neurotrophism, neuroprotection, neurotransmission, and neuroplasticity. Vitamin D exerts its biological function not only by influencing cellular processes directly, but also by influencing gene expression through vitamin D response elements."

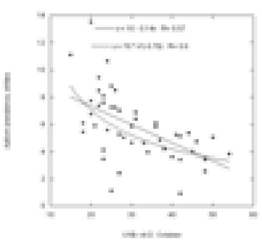
Neuroprotection – 2

- "This review highlights the epidemiological,
- neuropathological, experimental, and molecular genetic evidence implicating vitamin D as a candidate in influencing susceptibility to a number of psychiatric and neurological diseases. The strength of evidence varies for schizophrenia,
- autism, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and is especially strong for multiple sclerosis."
  - Deluca GC, Kimball SM, Kolasinski J, Ramagopalan SV, Ebers GC. The Role of Vitamin D in Nervous System Health and Disease. Neuropathol Appl Neurobiol. 2013 Aug;39(5):458-84.

Autism

- The UVB-vitamin D-autism hypothesis was proposed by John J. Cannell, M.D., in 2008:
  - Cannell JJ. Autism and vitamin D. Med Hypotheses. 2008;70(4):750-9.
- Since then, a number of studies have provided additional support for this hypothesis.

Autism Prevalence in U.S. vs. Solar UVB Doses for October



Grant WB, Cannell JJ. Autism prevalence in the United States with respect to solar ultraviolet-B doses: An ecological study. Dermatoendocrinol. 2013;5(1):

Autism

- It appears that both low 25(OH)D levels during pregnancy and in early life may be risk factors for the development of autism.
- It also appears that raising 25(OH)D levels can reduce the symptoms of autism.

- Cannell JJ. Autism, will vitamin D treat core symptoms? Med Hypotheses. 2013;81(2):195-8.

Autism, will vitamin D treat core symptoms? John J. Cannell

- Parents of autistic children who have access to swimming pool have reported summertime improvement in symptoms to me. A Japanese case report found the same summer times improvements. Vitamin D is highly seasonal with a summertime surfeit and a wintertime deficit. Recent research indicates that autism often first present itself during the second and third year of life. This is a time when most toddlers have no known sources of vitamin D.
- Vitamin D has remarkable antioxidant, anti-inflammatory, and anti-autoimmune properties. In vitro, in vivo, and animal experiments provide compelling data for vitamin D's role brain proliferation, differentiation, neurotrophism, neuroprotection,
- neurotransmission, and neuroplasticity. It also upregulates glutathione, upregulates a suit of genes involved in DNA repair and raises the seizure threshold. Adequate, perhaps pharmacological, doses of vitamin D may have a treatment effect in the core symptoms of autism.

Meta-analysis of All-Cause Mortality According to Serum 25-Hydroxyvitamin D

- Given that UVB and vitamin D have many health benefits, it is reasonable to think that those with higher 25(OH)D levels would have lower mortality rates. This expectation was reconfirmed in a paper published last week:
  - Cedric F. Garland, DrPH, June Jiwon Kim, BS, Sharif Burgette Mohr, MPH, PhD, Edward Doerr Gorham, MPH, PhD, William B. Grant, PhD, Edward L. Giovannucci, MD, ScD, Leo Baggerly, PhD, Heather Hofflich, DO, Joe Wesley Ramsdell, MD, Kenneth Zeng, BS, and Robert P. Heaney, MD. Am J Public Health. Published online ahead of print June 12, 2014: e1-e8. doi:10.2105/AJPH.

Randomized Controlled Trials

- RCTs are essential for pharmaceutical drugs to show both efficacy and lack of harm.
- Most vitamin D RCTs to date have been based on the pharmaceutical drug model (one source of agent, linear dose-response relation). These assumptions are not valid for vitamin D.
- Thus, the fact that many of the results from ecological, laboratory, and observational studies have not been confirmed from vitamin D RCTs conducted on populations with 25(OH)D levels above 20-25 ng/mL given 400-1000 IU/d vitamin D should not be considered evidence that vitamin D is not effective in reducing risk of disease.

Guidelines for optimizing design and analysis of clinical studies of Vitamin D

- Start with the 25(OH)D level-health outcome relation from observational studies.
- Measure 25(OH)D levels and only include those with low levels (<15-20 ng/mL)
- Supplement with sufficient vitamin D_3 to raise 25(OH)D levels to >40 ng/mL
- Also make sure that cofactors are optimized
- Remeasure 25(OH)D levels

- Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr Rev. 2014 Jan;72(1):48-54.

Conclusion

- There is strong evidence that having 25(OH)D levels above 30 ng/mL up to 50 ng/mL is associated with many health benefits for those with developmental disabilities.
- To reach those levels takes 1000-5000 IU/d vitamin D3 in the absence of frequent solar ultraviolet-B irradiance.

For more information:

- **www.grassrootshealth.net**
- **www.healthresearchforum.org.uk**
- **www.ncbi.nlm.nih.gov/pubmed/**
- **scholar.google.com**
- **www.sunarc.org**
- **www.vitamindcouncil.org**
- **http://www.vitamindsociety.org/**
- **www.vitamindwiki.com/VitaminDWiki**